39. (Reiterated) A method of modulating the binding of TWEAK to the TWEAK receptor in a mammal in need of such treatment, comprising administering to the mammal an inhibition-effective amount of a composition comprising a TWEAK receptor antagonist selected from the group consisting of : (a) a polypeptide comprising a soluble TWEAK receptor extracellular domain; and (b) an antibody that binds to the TWEAK receptor extracellular domain.

REMARKS

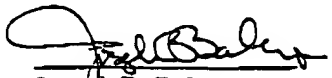
Claims 4-5, 24-38, and 40-45 have been canceled without prejudice to Applicant's right to prosecute the canceled subject matter in any divisional, continuation, continuation-in-part, or other application. Claims 1, 6, 8, 13, and 16 have been amended. Attached hereto is Appendix A, which shows the amendments made to the claims using standard notation (underlining and bracketing), the Appendix is captioned "Version with Markings to Show Changes." No new matter has been added.

The claims have been amended to correct dependencies consistent with the Response to the Restriction Requirement, to correct grammatical or typographical errors, and to maintain proper antecedent basis for claim-terms consistent with the Response to the Restriction Requirement. None of the foregoing amendments are in response to matters of patentability. Applicant respectfully requests allowance of the pending claims.

The Examiner is invited to call the undersigned attorney at (206) 389-4155 upon receipt and review of this Response to the Restriction Requirement to discuss any questions or concerns about the present response.

No fee is believed to be due with respect to the filing of the present paper.

Respectfully submitted,



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Appendix A

Version with Markings to Show Changes

1. (Amended) A method of modulating angiogenesis in a mammal in need of such treatment comprising administering a therapeutically-effective amount of a composition comprising an antagonist of a TWEAK receptor [antagonist or TWEAK receptor agonist], wherein the TWEAK receptor comprises a sequence as set forth from amino acids 28-79 of SEQ ID NO:7 or naturally occurring variants thereof.

2. (Reiterated) The method of claim 1 wherein the composition further comprises a pharmaceutically acceptable carrier.

3. (Reiterated) The method of claim 2 wherein the mammal is a human.

4. (Canceled) The method of claim 3 wherein the TWEAK receptor comprises a sequence selected from the group consisting of:

(a) amino acids 28-79 of SEQ ID NO:7; and

(b) naturally occurring variants of (a).

5. (Canceled) A method of inhibiting angiogenesis according to claim 4 wherein the composition comprises a TWEAK receptor antagonist.

6. (Amended) The method of claim [5] 1, wherein the antagonist is selected from the group consisting of a soluble TWEAK receptor fragment[s], [antibodies] an antibody, an antisense nucleic acid, [and] a triple helix forming nucleic acid[s], a peptide[s], and a small molecule[s].

7. (Reiterated) The method of claim 6 wherein the antagonist comprises a soluble TWEAK receptor fragment.

8. (Twice Amended) The method of claim 7, wherein the antagonist comprises:

(c) an Fc polypeptide, leucine zipper domain, and/or peptide linker; and

(d) about two to four polypeptides comprising a TWEAK receptor extracellular domain or fragments or variants thereof that are capable of binding TWEAK.

9. (Reiterated) The method of claim 8 wherein the antagonist comprises an Fc polypeptide fused to: (a) a TWEAK receptor extracellular domain; or (b) a fragment or variant of (a) that is capable of binding TWEAK.

10. (Reiterated) The method of claim 9 wherein the TWEAK receptor extracellular domain comprises amino acids 28-79 of SEQ ID NO:7.

11. (Reiterated) The method of claim 10 wherein the antagonist comprises amino acids 28-309 of SEQ ID NO:7.

12. (Reiterated) The method claim 6 wherein the antagonist comprises an antibody that binds specifically to the TWEAK receptor extracellular domain.

13. (Amended) The method of claim 12, wherein the antibody is selected from the group consisting of a monoclonal [antibodies] antibody, a humanized [antibodies] antibody, a transgenic [antibodies] antibody, and a human [antibodies] antibody.

14. (Reiterated) The method of claim 12 wherein the antibody is conjugated to a radioisotope, to a plant-, fungus-, or bacterial-derived toxin such as ricin A or diptheria toxin, or to another chemical poison.

15. (Reiterated) The method of claim 6 wherein the antagonist disrupts the interaction between the TWEAK receptor and a TRAF molecule.

16. (Amended) The method of claim [5] 2, wherein the mammal has a disease or condition mediated by angiogenesis.

17. (Reiterated) The method of claim 16 wherein the disease or condition is characterized by ocular neovascularization.

18. (Reiterated) The method of claim 16 wherein the disease or condition is a solid tumor.

19. (Reiterated) The method of claim 16 wherein the method further comprises treating the marumal with radiation.

20. (Reiterated) The method of claim 16 wherein the method further comprises treating the mammal with a second chemotherapeutic agent.

21. (Reiterated) The method of claim 20 wherein the second chemotherapeutic agent is selected from the group consisting of alkylating agents, antimetabolites, vinca alkaloids and other plant-derived chemotherapeutics, nitrosoureas, antitumor antibiotics, antitumor enzymes, topoisomerase inhibitors, platinum analogs, adrenocortical suppressants, hormones, hormone agonists, hormone antagonists, antibodies, immunotherapeutics, blood cell factors, radiotherapeutics, and biological response modifiers.

22. (Reiterated) The method of claim 20 wherein the second chemotherapeutic agent is selected from the group consisting of cisplatin, cyclophosphamide, mechloretamine, melphalan, bleomycin, carboplatin, fluorouracil, 5-fluorodeoxyuridine, methotrexate, taxol, asparaginase, vincristine, and vinblastine, lymphokines and cytokines such as interleukins, interferons (including alpha, beta, or delta), and TNF, chlorambucil, busulfan, carmustine, lomustine, semustine, streptozocin, dacarbazine, cytarabine, mercaptopurine, thioguanine, vindesine, etoposide, teniposide, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin, mitomycin, L-asparaginase, hydroxyurea, methylhydrazine, mitotane, tamoxifen, and fluoxymesterone.

23. (Reiterated) The method of claim 20 wherein the second chemotherapeutic agent is selected from the group consisting of Flt3 ligand, CD40 ligand, interleukin-2, interleukin-12, 4-1BB ligand, anti-4-1BB antibodies, TNF antagonists and TNF receptor

antagonists, TRAIL, CD148 agonists, VEGF antagonists, VEGF receptor antagonists, and Tek antagonists.

24. (Canceled) A method of promoting angiogenesis according to claim 4 wherein the composition comprises a TWEAK receptor agonist.

25. (Canceled) The method of claim 24 wherein the agonist is an agonistic antibody that binds specifically to the TWEAK receptor extracellular domain.

26. (Canceled) The method of claim 25 wherein the antibody is selected from the group consisting of monoclonal antibodies, humanized antibodies, transgenic antibodies, and human antibodies.

27. (Canceled) The method of claim 25 wherein the agonist is administered:

(a) to treat a vascularization deficiency in cardiac or peripheral tissue, including coronary artery disease, myocardial ischemia, myocardial infarction, angina pectoris, peripheral circulation deficits, limb ischemia/ reperfusion injury;

(b) to enhance wound healing, organ transplantation, reconnection of severed digits or limbs, or vascular or skin grafting; or

(c) in conjunction with bypass surgery or angioplasty.

28. (Canceled) An antagonist comprising:

(a) an Fc polypeptide, leucine zipper domain, or peptide linker; and

(b) a TWEAK receptor extracellular domain or fragment or variant thereof that is capable of binding TWEAK.

29. (Canceled) The antagonist of claim 28 wherein the TWEAK receptor extracellular domain comprises amino acids 28-79 of SEQ ID NO:7.

30. (Canceled) The antagonist of claim 28 wherein the antagonist comprises amino acids 28-309 of SEQ ID NO:7.

31. (Canceled) A nucleic acid encoding an antagonist according to claim 28.

32. (Canceled) An expression vector comprising the nucleic acid of claim 31.

33. (Canceled) A recombinant host cell comprising the nucleic acid of claim 31.

34. (Canceled) A method of producing a TWEAK receptor antagonist comprising culturing the host cell of claim 33 under conditions promoting expression of the antagonist.

35. (Canceled) A method of identifying a compound that is capable of modulating angiogenesis comprising:

(a) identifying a test compound that binds to a TWEAK receptor extracellular domain, wherein the test compound is not TWEAK;

(b) identifying a test compound that affects the interaction between a TWEAK and a TWEAK receptor; or

(c) identifying a test compound that modulates the interaction between a TWEAK receptor and a TRAF.

36. (Canceled) The method of claim 35 further comprising determining the ability of the test compound to modulate endothelial cell proliferation, endothelial cell migration, and/or angiogenesis.

37. (Canceled) The method of claim 35 wherein the modulation is stimulatory.

38. (Canceled) The method of claim 35 wherein the modulation is inhibitory.

39. (Reiterated) A method of modulating the binding of TWEAK to the TWEAK receptor in a mammal in need of such treatment, comprising administering to the mammal an inhibition-effective amount of a composition comprising a TWEAK receptor antagonist selected from the group consisting of : (a) a polypeptide comprising a soluble

TWEAK receptor extracellular domain; and (b) an antibody that binds to the TWEAK receptor extracellular domain.

40. (Canceled) A method for targeting a detectable label or chemotherapeutic to vascular tissue comprising contacting vascular tissue with an antibody that binds TWEAK receptor.

41. (Canceled) The method of claim 40 wherein the antibody is conjugated to a radioisotope, chemiluminescent or fluorescent compound, or enzyme.

42. (Canceled) The method of claim 40 wherein the antibody is conjugated to a cytotoxin.

43. (Canceled) The antagonist of claim 28, wherein the antagonist comprises about two to four polypeptides comprising a TWEAK receptor extracellular domain or fragments or variants thereof that are capable of binding TWEAK.

44. (Canceled) The recombinant host cell of claim 33, wherein the host cell is a prokaryote selected from the group consisting of *E. coli, Bacillus subtilis,* and *Salmonella typhimurium.*

45. (Canceled) A TWEAK receptor antagonist produced by the method comprising culturing the host cell of claim 33 under conditions promoting expression of the antagonist.

CERTIFICATE OF TRANSMISSION BY FACSIMILE (37 CFR 1.8)

I hereby certify that this Response to Restriction Requirement and Second Preliminary Amendment is being facsimile transmitted to the United States Patent and Trademark Office (Fax No. (703) 308-4315, Attention: Examiner Gary B. Nichol, Ph.D., Group Art Unit 1642 on the date indicated below.

Date: April 23, 2002 Signed: Elizabeth M. McCarthy
Elizabeth M. McCarthy